Detailed Action

This office action is a response to applicant's communication submitted July 10, 2008 wherein the rejections of record in the previous office action are traversed. This application claims benefit of provisional application 60/421003, filed October 24, 2002.

Claims 1-5, 9, 23, and 27-37 are pending in this application.

Claims 1-5, 9, 23, and 27-37 as amended are examined on the merits herein.

Applicant's arguments, submitted July 10, 2008, with respect to the rejection of instant claims 1, 9, 27-30, and 33-34 under 35 USC 103(a) for being obvious over Omoigui et al. in view of Olmarker et al. have been fully considered and found to be persuasive to remove the rejection as Olmarker et al. is seen to teach away from the claimed dosage range of 5-50 mg for the specific compound CDC-501. Therefore the rejection is withdrawn.

Applicant's arguments, submitted July 10, 2008, with respect to the rejection of instant claims 31 and 32 under 35 USC 103(a) for being obvious over Omoigui et al. in view of Olmarker et al. in view of Remington have been fully considered and found to be persuasive to remove the rejection as Olmarker et al. is seen to teach away from the claimed dosage range of 5-50 mg for the specific compound CDC-501. Therefore the rejection is withdrawn.

The following rejections of record in the previous office action are maintained:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 9, and 27-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Omogui et al. (US patent publication 2004/0038874, of record in previous action) in view of Muller et al. (US patent 6281230, of record in previous action).

Omoigui discloses a method for the treatment of persistent pain by administering a drug that antagonizes one or more mediators of inflammation. (p. 1, paragraph 0004) Drugs useful in this manner include TNF-α blockers, (p. 2, paragraphs 0007 and 0011) including thalidomide and analogues as a specific embodiment. (p. 3, paragraph 0023) Reflex Sympathetic Dystrophy, otherwise known as chronic regional pain syndrome, is listed as a disease treatable by this method. (pp. 9-10, paragraphs 0078-0082)

Omoigui does not disclose a method using the specific compounds of the claimed invention in the specific dosage amounts listed, in the dosage forms of instant claims 27-30 and 33-34.

Muller et al. discloses a range of isoindilyl-piperidines including the claimed structure, that decrease levels of TNF-α *in vivo*. (column 4 line 38 - column 5 line 11, wherein R_{1-3} = H, R_4 = NH_2, X = C=O, Y = CH_2, R_6 = H) These compounds can be used to inhibit the undesirable effects of TNF-α in an animal in need thereof, and can be

administered concurrently with an additional active agent. (column 5 lines 23-45) Dosage forms are disclosed having from 1-100 mg of drug per dose. (column 8, lines 27-35) The compound of the claimed invention, 3-(4-amino-1-oxoisoindolin-2-yl)piperidine-2,6-dione, is disclosed as one embodiment of the active agents useful in this therapeutic method. (column 17 example 16) The compounds disclosed by Muller et al. are chiral and can be purified by chiral adsorbant chromatography or chiral conjugation and used as their individual enantiomers. (column 8 lines 1-17)

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the therapeutic method of Omoigui using the compound 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione in the specific dosage amounts listed, in the dosage forms of instant claims 27-30 and 33-34. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Muller et al. discloses that the claimed compound is a TNF-α inhibitor and thus useful in the method of Muller. One of ordinary skill in the art would have also recognized that the compound of Muller is a thalidomide analog, based upon the fact that it shares a common isoindilyl-piperidine core structure with thalidomide. Therefore it would be seen to be useful as a thalidomide analog in the method of Omogui et al. One of ordinary skill in the art would have been motivated to administer the compound orally and in combination with other active agents because these limitations are taught by Muller et al. for this compound. One of ordinary skill in the art would have been motivated to administer a dosage of 5-50 mg because this dosage range overlaps substantially with the dosage range of 1-100 mg taught by Muller et al. One of ordinary

skill in the art would have been motivated to administer the compound as a tablet or capsule because these dosage forms are similar to the pill and lozenge oral dosage forms taught by Muller et al. One of ordinary skill in the art would have been motivated to administer the compounds as a pharmaceutically acceptable salt, solvate, or stereoisomer because these pharmaceutically acceptable dosage forms are routine and well known in the art for compounds to be administered as pharmaceuticals. One of ordinary skill in the art would have reasonably expected success in using this specific compound because Muller et al. already discloses that the compound can be used to treat other TNF-dependant disorders. One of ordinary skill in the art would have reasonably expected success in using the specific claimed dosage form and amounts because determining the exact details of the dosage form to be administered is well within the ordinary and routine level of skill in the art. With respect to the dosage ranges of claims 33-35, one of ordinary skill in the art would have been motivated to test various dosages in order to optimize the therapeutic regiment for the particular disease being treated. (e.g. complex regional pain syndrome) and the particular route of administration (e.g. oral vs. intravenous) This experimentation is merely routine and predictable.

Furthermore it would have been obvious for one of ordinary skill in the art to use the compounds of Muller et al. as individual enantiomers. One of ordinary skill in the art would have been motivated to do so because resolving and using individual enantiomers is specifically suggested by Muller et al. One of ordinary skill in the art

would reasonably have expected success because Muller et al. suggests specific ways of accomplishing the chiral separation.

Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted July 10, 2008, have been fully considered as regards the above grounds of rejection and not found to be persuasive to remove the rejection. Applicant argues that there is not a motivation in the prior art to use the specific compound recited in the claims and taught by Muller as a therapeutic compound for treating complex regional pain syndrome (CRPS). This compound is clearly taught by Muller as a TNF-alpha inhibitor, as discussed above. Therefore any defect in the prior art references must lie with Omogui. Applicant's traversal relies upon the assertion that Omogui's identification of TNF-alpha blockers such as thalidomide and thalidomide analogs as being useful for treating the identified pain disorders is somehow lacking. This argument appears to hinge on the large number of disorders and classes of compounds taught by Omogui. As indicated in the previous office action, the mere recitation of a large number of different alternatives by the prior art does not constitute a teaching away from any one particular alternative, or remove the expectation of success in practicing the invention. One of ordinary skill in the art would be able to practice any of the embodiments of Omogui et al. using the disclosed classes of compounds, for example TNF-alpha blocking thalidomide analogs, and furthermore to select any prior art disclosed TNF-alpha blocking thalidomide analogs to use in this method. Contrary to Applicant's assertion, the prior art specifically identifies CRPS as a disease species (Omoigui) and specifically identifies

the claimed compound CDC-501 as a therapeutic agent that inhibits TNF-alpha. (Muller) As regards the decision to use the particular compounds of Muller et al., these compounds are clearly disclosed as TNF-alpha blockers by Muller et al., and so would be clearly useful in this manner in the invention of Omogui. Furthermore one of ordinary skill on the art would regard them as being thalidomide analogs. Although, as discussed in the previous office action, the motivation to use these compounds in this manner is based primarily on their disclosed TNF-alpha blocking activity, the structural similarity to thalidomide, while not the primary factor in making the combination, is close enough to add to the expectation of success of one of ordinary skill in the art.

Specifically, Applicant points out that Omoigiu et al. never defines the term "thalidomide analog". While it is in fact the case that the exact metes and bounds of this term are not defined by the reference in such a way as to exactly specify the limits of what compounds are intended, one of ordinary skill in the art would be able to clearly determine that the claimed compound is a thalidomide analog. This compound has a structure that is clearly derived from thalidomide and differs only by the addition of an amino group and the deletion of an oxo group. Therefore the identification of TNF-alpha inhibiting thalidomide derivatives as therapeutic agents for CRPS would clearly motivate one of ordinary skill in the art to use this compound, which has a structure that is a clear derivative of thalidomide and is active as a TNF-alpha inhibitor.

Applicant further argues that Muller does not give a motivation or reasonable expectation of success for using the specific claimed enantiomer, citing *Forest Labs, INC vs. Ivax Pharmaceuticals, INC* to demonstrate that an isolated enantiomer can be

patentable over the racemic mixture. However, Muller does more than simply disclose the racemic mixture. Muller discloses a class of compounds having the same chiral carbon skeleton as the instantly claimed compound, as well as a specific compound which is identical to the racemate. Muller then specifically recognizes that these compounds have a chiral center, and explicitly suggests isolating and using the individual enantiomers. Muller then further suggests ways to isolate this enantiomer, including chiral chromatography and conjugation with a chiral acid. In view of this disclosure, one of ordinary skill in the art would clearly be motivated to use these individual enantiomers and would be able to isolate them by the suggested methods with a reasonable expectation of success. Doing so would not be a decision out of the blue to hunt for specific active enantiomers, but rather a decision to follow directions specifically laid out by the prior art reference.

For these reasons the rejection is deemed proper and maintained.

The following new grounds of rejection are introduced:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2-5 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Omoigui (US patent publication 20040038874, of record in previous action) in view

of Muller et al. (US patent 6020358, of record in previous action) as applied to claims 1, 9, 27-37 above, and further in view of Merck. (Reference included with PTO-892)

The disclosure of Omoigui in view of Muller et al. is discussed above. Omoigui in view of Muller et al. does not disclose a method further comprising administering the additional therapeutic agents of instant claims 2-5 or the therapies of instant claim 23.

Merck discloses that complex regional pain syndrome may be treated with several drugs including nifedipine, prednisone, opioid analgesics, tricyclic antidepressants, and anticonvulsants. (p. 1373, left column, second paragraph) It should be noted that it is well known in the art that opioid analgesics include oxycodone, tricyclic antidepressants include amitryptyline, imipramine, and doxepin, and anticonvulsants include gabapentin. Merck also discloses that physical therapy is essential throughout therapy for complex regional pain syndrome (p. 1373, left column, last paragraph) and that pain relief that outlasts the administration of a sympathetic block but is still transitory suggests the need for surgery. (p. 1373, left column, second paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the method of Omoigui et al. for the treatment of complex regional pain syndrome further comprising administering one or more of the pharmaceutical active agents described by Merck and still further administering physical therapy and/or surgery. One of ordinary skill in the art would have been motivated to combine these teachings because Omoigui et al. and Merck both disclose their respective teaching as being useful for treating the same condition, namely complex regional pain syndrome.

One of ordinary skill in the art would reasonably have expected success because combining two treatments known in the prior art to be effective for treating the same disorder by different methods is reasonably expected to produce at least additive effects.

Thus the invention taken as a whole is *prima facie* obvious.

Conclusion

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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